

**Department of Veterans Affairs  
Tuscaloosa VA Medical Center**

---

**Human Research Protection Program SOP #3**

**October 17, 2007**

---

**IRB INITIAL REVIEW**

**1. POLICY**

The Tuscaloosa VA Medical Center (TVAMC) Human Research Protection Program (HRPP) is committed to protecting the rights and welfare of human research subjects by outlining policy and delineating responsibility and procedures of the Institutional Review Board (IRB; also previously and elsewhere referred to as the Subcommittee on Human Studies).

It is the policy of the TVAMC HRPP to ensure that the applicable Federal, state, and local regulations are carried out in protecting the rights and welfare of subjects who voluntarily participate in investigational studies within this Medical Center. This Standard Operating Procedure (SOP) provides written policies and procedures for the information provided to the IRB for the initial review of research, for conducting initial reviews of research proposals and for communicating its findings and actions to the TVAMC Director, Research and Development (R&D) Committee, and the investigator.

**2. RESPONSIBILITIES**

**The TVAMC Director** is responsible for making final decisions approving research studies based on recommendations from the IRB at the time of initial review.

**The TVAMC R&D Committee** makes recommendations to the Director for approval or disapproval of the actions of the IRB.

**The TVAMC IRB** is responsible for the initial review and subsequent continuing reviews of investigational studies involving human participants. It makes recommendations concerning approval, disapproval, modifications, restrictions, suspensions, or termination of such studies to the R&D Committee. Within the review process, the committee is responsible for safeguarding human studies in the areas of informed consent, voluntary participation, confidentiality, and ensures that human experimentation is performed under stipulation and procedures of the written protocol as approved.

**Principal Investigators** are responsible for submitting the research proposal to the IRB for evaluation and decision before initiation. Under no circumstances may an investigator begin a study involving human participation without approval from the IRB, the R&D Committee, and the Director, who endorses the R&D Committee Minutes.

### 3. DEFINITIONS

See HRPP SOP#2 for definitions of “research” and “human subject.”

### 4. PROCEDURES

- a. General Procedures.** Unless determined to be exempt (HRPP SOP #5), all human subject research conducted at the TVAMC or by TVAMC employees must be prospectively reviewed, as described below, and approved by the IRB. No human subject research may be initiated or continued at the TVAMC or by TVAMC employees without prospective approval by the IRB. If an investigator is unsure whether IRB review is required, he/she is required to consult with the IRB Chair or C/R&D and may be asked to submit a detailed letter explaining his/her plans and request a determination from the IRB on whether or not the study meets the regulatory definition of human research.

The IRB chair (or designee) will determine whether a proposed research project meets the definition of human subject's research (and therefore requires IRB review). In making this assessment, the IRB Chair (or designee) will use the flowchart in the Addendum to determine if the following are true statements regarding the proposed research project:

- a. The proposed activity is a *systematic* investigation designed to develop or contribute to *generalizable* knowledge (and is therefore research).
- b. The proposed activity involves obtaining information through intervention or interaction with living individuals OR obtaining identifiable private information about living individuals (and therefore involves human subjects).
- c. The proposed activity involves administration of a *test article* (e.g., experimental drug or medical device) to one or more persons and is subject to the requirements for prior submission to the Food and Drug Administration under sections 505(i) or 520(g) of the Food, Drugs, and Cosmetics Act (and therefore meets the FDA definition of research).

If a proposed activity is determined to be research involving human subjects or the administration of a test article, human subjects protection is necessary and the activity is subject to review by the IRB and the R&D (as detailed in these SOPs). If a proposed activity is determined to be research but DOES NOT involve human subjects or the administration of a test article, it is subject to review by R&D, but human subject's protection is NOT necessary and the activity is NOT subject to review by the IRB. If a proposed activity is determined NOT TO BE research, the activity is subject to review by NEITHER the IRB NOR the R&D.

Regardless of the type of review (approval as exempt, expedited or reviewed at a convened meeting), the investigator is notified in writing of the IRB's determination.

For an in depth review, the TVAMC uses a primary reviewer system described in HRPP SOP #2 and documentation of that review is provided on the Primary Review Checklist form. If a protocol is submitted for review and the primary reviewer or other IRB

members believe that there is insufficient information to enable an appropriate review, a written request for additional information may be sent to the Principal Investigator. Regardless of the type of review (approval as exempt, expedited or reviewed at a convened meeting), the investigator is notified in writing of the IRB's determination.

- b. Documents Required for Initial Review (See Checklist of Documents for Initial Review).** Prior to the convened meeting, all members of the IRB shall be provided with sufficient information to substantially and meaningfully evaluate the proposed research and determine appropriate action during the convened meeting. The list of documents that the investigator must submit for initial review are listed in the Checklist of Documents for Initial Review. The investigator must submit all materials to the IRB Staff 14 days prior to the next IRB meeting. The agenda and all supporting documentation to be reviewed are made available to all IRB members ideally within 7 days, but no less than 4 days, in advance of the meeting.

In addition to the agenda and the previous month's minutes, all members receive the following for each study considered for initial review:

- Abstract
- Protocol (TVAMC format)
- Informed Consent Form (VA form 10-1086) and HIPPA statement or request of waiver and HIPPA waiver
- Investigational Drug Information Record (10-9012)
- Investigators' Financial Disclosure and Conflict of Interest Forms
- Recruitment or advertising material(s), if applicable
- Other materials needed to support the agenda
- If not already on file in the IRB office, a copy of the curriculum vitae and certificates of completion on the protection of human subjects in research and Good Clinical Practices (and other required training in HRPP SOP #12) for Investigators and Co-investigators
- Subject surveys or questionnaires, if not a standardized rating scale

At initial review, the primary reviewer also receives these applicable materials, (which are available in the IRB office and at the meeting for all other members to review upon request):

- Any relevant Merit reviews or grant applications
- Investigator's Brochure or equivalent material (package insert), if drug is involved
- Full sponsor protocol, if applicable

- c. Protocol Requirements:** In order to judge if criteria are met the IRB needs the following detailed information to be included in the protocol and the IRB documents its consideration of these elements in the primary reviewer checklist (see Primary Review Checklist).

1. Title of the study (175 characters maximum)
2. Principal Investigator

3. All co-investigators
4. Sponsor of the study
5. Research setting
6. Purpose of the study including hypothesis to be tested
7. Background, including results of relevant research, gaps in the current knowledge.
8. Potential benefits to the research subject and the knowledge to be gained (Choose from the following: Prospect for direct benefit to participants [include knowledge to be gained], Little prospect for benefit to participants, but likely to yield generalizable knowledge, No prospect for direct benefit to participants, but likely to yield generalizable knowledge, No prospect for direct benefit to participants, and unlikely to yield generalizable knowledge)
9. Definition of population to which study is directed and justification
10. Number of the subjects that will be recruited for study
11. Subject inclusion/selection criteria
12. Subject exclusion criteria
13. Subject exit criteria
14. Justification for use of special subject populations who may present informed consent issues (for example, incompetent patients, elderly, etc.) and reason for inclusion
15. Scientific and ethical justification for excluding classes (gender, race, etc) of persons who might benefit from the research
16. Appropriateness of Impact of Study design on risk
17. Description of procedures to be performed
18. Description of the anticipated data and how the data will be analyzed to test the specific hypotheses
19. Risks (physical, psychological, social, and economic) and steps taken to minimize these risks (all four types of risk must be stated in consent form)
20. Provisions for managing adverse reactions and for monitoring data to ensure the safety of participants
21. Planned procedure for obtaining informed consent including the circumstances surrounding consent procedures including: setting, subject autonomy concerns, language difficulties, cultural differences, educational capabilities, and vulnerable populations, when applicable. Also include the procedures for documentation of Informed Consent.
22. Compensation for participation, if offered, and amount (include when participant will be paid i.e., after each visit, at end of study, etc.)
23. Plans for protection of patient confidentiality and privacy. The provisions to protect privacy may include use of a private office for interviewing, removing identifiable information, coding data, securing or limiting access to data, and obtaining Federal Certificate of Confidentiality. Also, a description of the use of personally identifiable records, the methods to protect the confidentiality of research data, and whether or not there is a Federal Certificate of Confidentiality in place, should be included in the HIPAA authorization form as part of the Informed Consent. The following issues must be addressed: Will the investigator collect individually identifiable information that may be transferred or transmitted to the Sponsor or outside the Tuscaloosa VA Medical Center? Clearly delineate

how the data will be secured and stored? Explain how the Patient Health Information will be destroyed when it is no longer needed?

24. Methods used to identify and recruit patients. These provisions include a description of the methods used to obtain information about subjects and/or those individuals who may be recruited to participate in studies. The methods may include surveys, questionnaires, interview, direct observation, rating scales, record review, tests, etc.
  25. Safeguards to prevent coercion or undue influence for study participants.
  26. Resources
  27. Safeguards to protect the rights and welfare of mentally disabled and/or decisionally impaired subjects (vulnerable patient populations)
  28. Plans for Adherence to VA Policies and Regulations Regarding Research Involving Controlled Drugs. [\HRPP Policies\Use of Controlled Substance in Research 102706.TIF](#): All Tuscaloosa VA Medical Center (TVAMC) policies and regulations and all other VHA policies regarding research involving controlled substances/drugs will be followed.
  29. References
- d. Criteria for IRB Approval:** Research with human subjects must be performed under stipulation and procedures of a written protocol, which has successfully met the test of peer review and has been approved by the IRB. The IRB should systematically evaluate the likelihood and magnitude of risks and potential benefits and knowledge to be gained. The IRB must evaluate and identify the risks that may result from the research and the steps taken to minimize risks and determine if potential gain outweigh potential risks in a research protocol. The IRB addresses many complex, overlapping, and intermingled issues dealing with the basic question, "is there any possible benefit from this study and does the potential gain outweigh the potential risk?" Risks to which research subjects may be exposed may be classified as physical, psychological, social, and economic.

Based on a review of the investigator's curriculum vitae (CV), past research experience listed in the CV, and training certificates, the IRB also evaluates whether the investigator is knowledgeable about FDA requirements, if the study involves an investigational drug.

Criteria for IRB approval include a determination and documentation of its consideration on the primary reviewer checklist that:

1. Risks to subjects are minimized, including physical, psychological, social, or economic. For example, risks can be minimized by using procedures that 1) are consistent with sound research, 2) do not unnecessarily expose participants to risk, 3) already being performed on the participants for diagnostic or treatment purposes, and 4) mitigate or reduce the risk.
2. The rights and welfare of human subjects will in every case supersede the interest of the investigator in experimentation.
3. Risks to subjects are reasonable in relation to anticipated benefit to subjects (if any) and the importance of the knowledge to be gained that may be expected to result from the research
4. All known risks are included in the Consent Form, and sponsors and PIs have not

used language that inappropriately minimizes risks and exaggerates potential benefits. The IRB distinguishes the risk of research activities from the risk of therapeutic activities (where applicable). See HRPP SOP #7 Research Informed Consent.

5. Selection of subjects is equitable, which includes the consideration of the following: purposes and setting of the research, the scientific and ethical justification for including vulnerable populations or for excluding classes of persons who might benefit from the research. See HRPP SOP #7 and SOP #8.
6. Informed Consent is adequate and is appropriately documented. A significant part of the initial review process focuses on the Consent Form. Research with human subjects must be done with proper Informed Consent. Informed Consent requires that the person consenting be given sufficient details in language that the person can understand to arrive at a decision in his own best interest. The language of the information in the document should neither be exculpatory or coercive. Additional elements of information may be required to be included in an Informed Consent when the opinions of the sponsor, the PI, or the IRB deem it necessary or appropriate. See HRPP SOP # 7 Research Informed Consent for more detail.
7. Adequate provisions are in place for monitoring research data collected (e.g., SAEs - both events at the TVAMC and sponsor reports of events at other sites, serious and unexpected events, subject enrollment and withdrawal etc.) to ensure the safety of subjects. This includes the plan for data and safety monitoring either by the research team or an independent Data and Safety Monitoring Board (DSMB).
8. Adequate provisions are in place to protect the privacy of subjects and to maintain the confidentiality of data. See HRPP SOP #10 Research Data Security and Privacy.
9. Appropriate safeguards have been included to protect the rights and welfare of vulnerable subject populations, which may include mentally challenged or incompetent, institutionalized, inpatients receiving care for long-term chronic illness (including Spinal Cord and Nursing Home), terminally ill (including cancer, HIV, genetic studies), employees, and students. The TVAMC does not conduct research on prisoners, children, pregnant women (as focus of research), fetuses, or neonates. See HRPP SOP #8 and SOP #7.
10. Certain studies may require special attention including:
  - a) Withdrawal of therapy, whether or not it is replaced by experimental treatment, when there is significant risk of morbidity or mortality.
  - b) Any invasive surgical procedure (including arterial catheterization), even if the experimental procedure replaces a standard surgical procedure that is thought to involve higher risk.
  - c) Significant risk of serious impairment.
  - d) Risks when there is no potential clinical benefit to the subject. (e.g. Phase I studies).

The risks should be thoroughly explained in the protocol and also in the consent form. Specific examples and explanation of these risks are described below.

**Physical Harms.** Medical research often involves exposure to minor pain, discomfort, or injury from invasive medical procedures, or harm from possible side effects of drugs. Some of the adverse effects that result from medical procedures or drugs can be permanent, but most are transient. Procedures commonly used in medical research usually result in no more than minor discomfort (*e.g.*, temporary dizziness, the pain associated with venipuncture). Some medical research is designed only to measure more carefully the effects of therapeutic or diagnostic procedures applied in the course of caring for an illness. Such research may not entail any significant risks beyond those presented by medically indicated interventions. On the other hand, research designed to evaluate new drugs or procedures may present more than minimal risk, and on occasion, can cause serious or disabling injuries.

**Psychological Harms.** Participation in research may result in undesired changes in thought processes and emotion (*e.g.*, episodes of depression, confusion, or hallucination resulting from drugs, feelings of stress, guilt, and loss of self esteem). These changes may be transitory, recurrent, or permanent. Most psychological risks are minimal or transitory, but some research has the potential for causing serious psychological harm. Stress and feelings of guilt or embarrassment may arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics such as drug use, sexual preferences, selfishness, and violence. These feelings may be aroused when the subject is being interviewed or filling out a questionnaire. Stress may also be induced when the researchers manipulate the subjects' environment - as when "emergencies" or fake "assaults" are staged to observe how passersby respond. Psychological harm may also result from behavioral research that involves an element of deception, particularly if the deception includes false feedback to the subjects about their own performance. Invasion of privacy is a risk of a somewhat different character. In the research context, it usually involves either covert observation or "participant" observation of behavior that the subjects consider private. Breach of confidentiality is sometimes confused with invasion of privacy, but it is really a different problem. Invasion of privacy concerns access to a person's body or behavior without consent; confidentiality of data concerns safeguarding information that has been given voluntarily by one person to another. A breach of confidentiality may result in psychological harm to individuals (in the form of embarrassment, guilt, stress, and so forth) or in social harm.

**Social and Economic Harms.** Some invasions of privacy and breaches of confidentiality may result in embarrassment within the subject's business or social group, loss of employment, or criminal prosecution. Areas of particular sensitivity are information regarding alcohol or drug abuse, mental illness, illegal activities, and sexual behavior. Some social and behavioral research may yield information about individuals that could "label" or "stigmatize" the subjects (*e.g.*, as actual or potential delinquents or schizophrenics). Confidentiality safeguards must be strong in these instances. The fact that a person has participated in HIV-related drug trials or has been hospitalized for treatment of mental illness could adversely affect present or future employment, eligibility for insurance, political campaigns, and standing in the community. Participation in research may result in additional actual costs to individuals. Any anticipated costs to research participants should be described to prospective subjects during the consent process. The IRB must seek information about risks to subjects and note when no risk exists. Even if a research study involves no risk, the

IRB must consider this during risk/benefit analysis.

**Mitigators of risks and provisions for safety monitoring** should be explained in the protocol. Risks to subjects can be minimized: 1) by using procedures that are consistent with sound research design that do not unnecessarily expose subjects to risk, and 2) by using procedures being performed for diagnosis and/or treatment. The study design can increase or decrease the risk of the study (overall) by exposing varying numbers of subjects to the risks of the study (determined by the study design and required sample size). While the particular risks to an individual subject may not be affected by the statistical design, exposing subjects to unnecessary risks can be. A fundamental consideration in all clinical trials is the safety of those who would be at potential risk from their participation in the trial. All clinical trials require safety monitoring, but not all trials require monitoring by a formal committee. For FDA regulated studies, Data Monitoring Committees (DMC) have generally been established for large, randomized multi-site studies with mortality or major morbidity as a primary or secondary endpoint. NIH requires data and safety monitoring, generally, in the form of Data and Safety Monitoring Boards (DSMB) for Phase 3 clinical trials. For earlier trials (Phases 1, 2), a DSMB may be appropriate if the study has multiple clinical sites, if it is blinded (masked), or if it employs particularly high-risk interventions or vulnerable populations.

- e. Determination that the Medical Record has to be Flagged: After a participant signs informed consent, the investigator must enter a clinical warning in the research participants chart (i.e. flagged chart) as a means to indicate participation in a study and the source of more information regarding the study, unless otherwise determined by the IRB that the medical record does not require a clinical warning (i.e. flagged) to protect the participant's safety. Such determination that a medical record does not warrant a clinical flag includes, but is not limited to, 1) the study involves only one encounter; 2) the study only involves the use of a questionnaire, 3) the study only involves the use of previously collected biological specimens or data, or 4) the identification of the patient as a subject in a particular study would place the subject at greater than minimal risk.
- f. **IRB Approval Letter/Memo and Conditions of IRB Approval:** The IRB Approval Letter includes a notice of approval with dates of approval (beginning the day that IRB approved the study with full or contingent approval) and expiration, continuing review interval, IRB determination is the medical record does not need to be flagged (see section d. above) and the following Conditions of IRB Approval and the Penalties for Noncompliance:

**Conditions of IRB Approval:**

1. Adhere to ethical principles: (1) Respect for persons - consent, privacy, confidentiality, (2) Beneficence - maximizes possible benefits to the subject and minimize possible harms, and (3) Justice - equitable selection.
2. Obtain informed, written consent by the investigator for each human subject or his/her legally qualified guardian or next-of-kin, unless specifically waived by the IRB. If the patient lacks decision-making capacity or has been declared incompetent, surrogate consent is required.



3. Document the Informed Consent Form in the medical record. A copy of the informed consent form may be scanned into the electronic medical record or a hard copy may be delivered to the Medical Records Department. In addition, the original signed Informed Consent Form is filed in the subject's case history binder, a copy of the signed Informed Consent Form is given to the subject or the subject's legal representative, and for those studies involving study medication, a copy of the signed Informed Consent Form is filed in the pharmacy research medication study binder.
4. Report any serious adverse event (SAE) or unexpected adverse event (UAE) or outcomes of this study in writing by the investigator to the IRB, whether or not these are attributed to the research project itself or to unrelated factors (both events at the TVAMC and sponsor reports of events at other sites). The FDA defines Serious Adverse Events (21CFR312.32) (SAEs) as: (1) death, (2) life-threatening, (3) hospitalization-initial or prolonged, (4) persistent or significant disability or incapacity, (5) congenital anomaly and/or birth defects, or (6) an important medical event (based upon appropriate medical judgment) that may jeopardize the subject and may require medical or surgical intervention to prevent permanent one of the outcomes listed in this definition.. In addition, serious or unexpected adverse reactions to drugs must be reported to the Committee on Pharmacy and Therapeutics.
5. Promptly report all deviations (including error and accidents) from the approved protocol and do not initiate any unapproved changes (amendments, consent form modifications, advertisements) without IRB review and approval, except where necessary to eliminate apparent immediate hazard to human subjects.
6. Investigators are reminded that they are personally responsible for the careful, thoughtful execution of studies involving human subjects. Conscious disregard of subject's rights as outlined in the Consent Form or failure to comply with all safeguards listed in the protocol will be met with severe sanctions.
7. If applicable, provide a copy of the Investigational Drug Information Record (VA Form 10-9012) to the Pharmacy Department prior to study initiation and request to receive, store, and dispense study medications. (The Pharmacy Department is responsible for the storage and dispensing of drugs).
8. Submit Continuing Review information to the IRB by the date specified and inform the IRB when your study is completed (federal law requires that every protocol must be reviewed a minimum of once per year). File a final report upon completion or termination of a study.
9. Submit all research manuscripts pertaining to this approved study to the R&D Committee for review and approval.

**Penalties for Noncompliance:**

1. Noncompliance may result in suspension of approval for a particular project. Serious or continuing noncompliance may result in suspension of the investigator's privilege to conduct research at this VAMC.
2. The TVAMC IRB is required to report items listed in the VA memo dated 11/12/2003 regarding "What to report to ORO".

**5. REFERENCES**

**6. ATTACHMENTS**

Checklist of Documents for Initial Review  
Primary Review Checklist

**7. RESCISSIONS**

HRPP SOP#3 dated May 7, 2007

**8. REVIEW DATE**

January 1, 2012

Signature on File in R&D Office

Lori L. Davis, MD

Coordinator of Research and Development